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     $0.11  Estimated total session cost   0.209 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1951-2005/Aug 31
         (c) format only 2005 Dialog
  File  55:Biosis Previews(R) 1993-2005/Aug W4
         (c) 2005 BIOSIS
  File  34:SciSearch(R) Cited Ref Sci 1990-2005/Aug W4
         (c) 2005 Inst for Sci Info
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
  File 340:CLAIMS(R)/US Patent 1950-05/Aug 30
         (c) 2005 IFI/CLAIMS(R)

      Set  Items  Description
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? S TRAIL
      S1   15693  TRAIL
? S ETOPOSIDE
      S2   39281  ETOPOSIDE
? S S1 AND S2
           15693  S1
           39281  S2
      S3     222  S1 AND S2
? S APOTO?
      S4     658  APOTO?
? S S3 AND S4
             222  S3
             658  S4
      S5       0  S3 AND S4
? S APOPTO?
      S6  370275  APOPTO?
? S S3 AND S6
             222  S3
          370275  S6
      S7     205  S3 AND S6
? S S7 AND PY<2000
Processing
             205  S7
        37631730  PY<2000
      S8       4  S7 AND PY<2000
? RD
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S9       4  RD (unique items)
? T S9/3,K,AB/1-4

 9/3,K,AB/1     (Item 1 from file: 55)
DIALOG(R)File  55:Biosis Previews(R)
(c) 2005 BIOSIS. All rts. reserv.

0012326806   BIOSIS NO.: 200000045119
Novel anti-leukemic strategy combining  TRAIL  (Apo2 ligand) and
  antileukemic cytotoxic drugs, Ara-C,  etoposide  or doxorubicin
AUTHOR: Wen Jinghai (Reprint); Nguyen Diep (Reprint); Fang Guofu (Reprint);
  Perkins Charles (Reprint); Orlando Mariangelli (Reprint); Jing Xin
  (Reprint); Bhalla Kapil (Reprint)
```

AUTHOR ADDRESS: Clinical and Translational Research, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA**USA
JOURNAL: Blood 94 (10 SUPPL. 1 PART 1): p278a Nov. 15, 1999 **1999**
MEDIUM: print
CONFERENCE/MEETING: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999; 19991203
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

Novel anti-leukemic strategy combining TRAIL **(Apo2 ligand) and antileukemic cytotoxic drugs, Ara-C,** etoposide **or doxorubicin 1999**
...REGISTRY NUMBERS: **etoposide**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **TRAIL** ; ...

... **etoposide** --
MISCELLANEOUS TERMS: **apoptosis** ;

9/3,K,AB/2 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2005 BIOSIS. All rts. reserv.

0011983904 BIOSIS NO.: 199900243564
Regulation of TRIAL and CD95/Fas/APO-1 gene expression by ionizing radiation in human leukemia cells
AUTHOR: Gong B; Almasan A
AUTHOR ADDRESS: Dep. Cancer Biol. Radiat. Oncol., Cleveland Clin. Found., Cleveland, OH, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40 p420 March, 1999 **1999**
MEDIUM: print
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999; 19990410
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

1999
...REGISTRY NUMBERS: **etoposide**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **etoposide** --...

...human **TRAIL** gene
MISCELLANEOUS TERMS: **apoptosis** ;

9/3,K,AB/3 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
(c) 2005 BIOSIS. All rts. reserv.

0011922729 BIOSIS NO.: 199900182389
Molecular determinants of response to TRAIL **combined with chemotherapy in**

killing of normal and cancer cells
AUTHOR: Kim K H; El-Deiry W S
AUTHOR ADDRESS: Howard Hughes Med. Inst., U. Penn., Philadelphia, PA 19104, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40 p486 March, 1999 **1999**
MEDIUM: print
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999; 19990410
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Molecular determinants of response to TRAIL **combined with chemotherapy in killing of normal and cancer cells**
1999
...REGISTRY NUMBERS: **etoposide** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **etoposide** --...

...TNF-related **apoptosis** inducing ligand {tumor necrosis factor-related **apoptosis** inducing ligand

9/3,K,AB/4 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0011915358 BIOSIS NO.: 199900175018
TRAIL **-R2 consist of two separate forms that are coordinately regulated**
AUTHOR: Wang T (Reprint)
AUTHOR ADDRESS: Basic Res. Lab., DBS, NCI-FCRDC, Frederick, MD 21702-1201, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40 p168-169 March, 1999 **1999**
MEDIUM: print
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999; 19990410
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

TRAIL **-R2 consist of two separate forms that are coordinately regulated**
1999
...REGISTRY NUMBERS: **etoposide**
DESCRIPTORS:
...ORGANISMS: **apoptosis** , human breast cancer cells

```
S1       15693   TRAIL
S2       39281   ETOPOSIDE
S3         222   S1 AND S2
S4         658   APOTO?
S5           0   S3 AND S4
S6      370275   APOPTO?
S7         205   S3 AND S6
S8           4   S7 AND PY<2000
S9           4   RD (unique items)
S10       5623   S2 AND S6
? S S7 AND PY<=2000
Processing
              205  S7
         39868366  PY<=2000
     S11       23  S7 AND PY<=2000
? RD
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S12       16  RD (unique items)
? S S12 NOT S9
               16  S12
                4  S9
     S13       12  S12 NOT S9
? T S13/3,K,AB/1-12

 13/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2005 Dialog. All rts. reserv.

13113384   PMID: 11090076
  Antileukemic drugs increase death receptor 5 levels and enhance
Apo-2L-induced apoptosis of human acute leukemia cells.
  Wen J; Ramadevi N; Nguyen D; Perkins C; Worthington E; Bhalla K
  Division of Clinical and Translational Research, Sylvester Comprehensive
Cancer Center, University of Miami School of Medicine, Miami, FL, USA.
  Blood (UNITED STATES) Dec 1 2000 , 96 (12) p3900-6, ISSN 0006-4971
Journal Code: 7603509
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  In present studies, treatment with tumor necrosis factor (TNF)-related
apoptosis inducing ligand ( TRAIL , also known as Apo-2 ligand [Apo-2L])
is shown to induce apoptosis of the human acute leukemia HL-60, U937, and
Jurkat cells in a dose-dependent manner, with the maximum effect seen
following treatment of Jurkat cells with 0.25 microg/mL of Apo-2L (95.0%
+/- 3.5% of apoptotic cells). Susceptibility of these acute leukemia cell
types, which are known to lack p53(wt) function, did not appear to
correlate with the levels of the apoptosis -signaling death receptors
(DRs) of Apo-2L, ie, DR4 and DR5; decoy receptors (DcR1 and 2); FLAME-1
(cFLIP); or proteins in the inhibitors of apoptosis proteins (IAP)
family. Apo-2L-induced apoptosis was associated with the processing of
caspase-8, Bid, and the cytosolic accumulation of cytochrome c as well as
the processing of caspase-9 and caspase-3. Apo-2L-induced apoptosis was
significantly inhibited in HL-60 cells that overexpressed Bcl-2 or
Bcl-x(L). Cotreatment with either a caspase-8 or a caspase-9 inhibitor
suppressed Apo-2L-induced apoptosis . Treatment of human leukemic cells
```

with **etoposide** , Ara-C, or doxorubicin increased DR5 but not DR4, Fas, DcR1, DcR2, Fas ligand, or Apo-2L levels. Importantly, sequential treatment of HL-60 cells with **etoposide** , Ara-C, or doxorubicin followed by Apo-2L induced significantly more **apoptosis** than treatment with Apo-2L, **etoposide** , doxorubicin, or Ara-C alone, or cotreatment with Apo-2L and the antileukemic drugs, or treatment with the reverse sequence of Apo-2L followed by one of the antileukemic drugs. These findings indicate that treatment with **etoposide** , Ara-C, or doxorubicin up-regulates DR5 levels in a p53-independent manner and sensitizes human acute leukemia cells to Apo-2L-induced **apoptosis** . (Blood. 2000;96:3900-3906)

Antileukemic drugs increase death receptor 5 levels and enhance Apo-2L-induced apoptosis **of human acute leukemia cells.**

Dec 1 **2000** ,

In present studies, treatment with tumor necrosis factor (TNF)-related **apoptosis** inducing ligand (**TRAIL** , also known as Apo-2 ligand [Apo-2L]) is shown to induce **apoptosis** of the human acute leukemia HL-60, U937, and Jurkat cells in a dose-dependent...

...Jurkat cells with 0.25 microg/mL of Apo-2L (95.0% +/- 3.5% of **apoptotic** cells). Susceptibility of these acute leukemia cell types, which are known to lack p53(wt) function, did not appear to correlate with the levels of the **apoptosis** -signaling death receptors (DRs) of Apo-2L, ie, DR4 and DR5; decoy receptors (DcR1 and 2); FLAME-1 (cFLIP); or proteins in the inhibitors of **apoptosis** proteins (IAP) family. Apo-2L-induced **apoptosis** was associated with the processing of caspase-8, Bid, and the cytosolic accumulation of cytochrome c as well as the processing of caspase-9 and caspase-3. Apo-2L-induced **apoptosis** was significantly inhibited in HL-60 cells that overexpressed Bcl-2 or Bcl-x(L). Cotreatment with either a caspase-8 or a caspase-9 inhibitor suppressed Apo-2L-induced **apoptosis** . Treatment of human leukemic cells with **etoposide** , Ara-C, or doxorubicin increased DR5 but not DR4, Fas, DcR1, DcR2, Fas ligand, or Apo-2L levels. Importantly, sequential treatment of HL-60 cells with **etoposide** , Ara-C, or doxorubicin followed by Apo-2L induced significantly more **apoptosis** than treatment with Apo-2L, **etoposide** , doxorubicin, or Ara-C alone, or cotreatment with Apo-2L and the antileukemic drugs, or...

... Apo-2L followed by one of the antileukemic drugs. These findings indicate that treatment with **etoposide** , Ara-C, or doxorubicin up-regulates DR5 levels in a p53-independent manner and sensitizes human acute leukemia cells to Apo-2L-induced **apoptosis** . (Blood. 2000;96:3900-3906)

Descriptors: *Antineoplastic Agents--pharmacology--PD; * **Apoptosis** --drug effects--DE; *Leukemia--pathology--PA; *Membrane Glycopro

3/3,K,AB/11 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08742919 Genuine Article#: 323VU Number of References: 25
Title: Coordinated regulation of two TRAIL -R2/KILLER/DR5 mRNA isoforms by DNA damaging agents, serum and 17 beta-estradiol in human breast cancer cells (ABSTRACT AVAILABLE)
Author(s): Wang TTY (REPRINT) ; Jeng JJ
Corporate Source: ARS,PHYTONUTRIENTS LAB, BELTSVILLE HUMAN NUTR RES CTR, USDA, BLDG 307, ROOM 326/BELTSVILLE//MD/20705 (REPRINT)
Journal: BREAST CANCER RESEARCH AND TREATMENT, **2000** , V61, N1 (MAY), P 87-96
ISSN: 0167-6806 Publication date: 20000500
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: A search of the Genebank database revealed that there are two distinct gene sequences with the common name of **TRAIL** -R2/Killer/DR5. Using reverse transcription-polymerase chain reaction (RT-PCR), we confirmed the existence of two isoforms of **TRAIL** -R2/Killer/DR5 mRNA, which we have designated the long and short isoforms based on their electrophoretic mobility. We found that both the long and short mRNA isoforms are ubiquitously expressed in human tissues and cell lines. The long form generally predominates, but the proportion of the two isoforms varies depending on the tissue type. Treatment of MCF-7 human breast cancer cells with the DNA damaging drugs adriamycin, campthothecin, or **etoposide** causes a coordinated up-regulation of both isoforms. Treatment of the p53-mutant T-47D breast cancer cell line with adriamycin also results in up-regulation of both isoforms, suggesting that adriamycin up-regulates **TRAIL** -R2/Killer/DR5 expression independent of functional p53. The expression of both mRNA isoforms are increased in MCF-7 cells cultured in charcoal-stripped fetal bovine serum compared to normal serum, suggesting that sex steroid hormones may play a role in the negative regulation of their expression. This was confirmed in MCF-7 cells cultured in stripped serum supplemented with 17 beta-estradiol, which also resulted in a decrease in the mRNA expression of both isoforms. These results demonstrate that the **TRAIL** -R2/Killer/DR5 gene gives rise to two distinct forms of mRNA, and that these two forms are coordinately regulated by DNA damage and 17 beta-estradiol in human breast cancer cells. The functional significance of the two isoforms remains to be determined.

Title: Coordinated regulation of two TRAIL -R2/KILLER/DR5 mRNA isoforms by DNA damaging agents, serum and 17 beta-estradiol in...
, **2000**
...Abstract: Genebank database revealed that there are two distinct gene sequences with the common name of **TRAIL** -R2/Killer/DR5. Using reverse transcription-polymerase chain reaction (RT-PCR), we confirmed the existence of two isoforms of **TRAIL** -R2/Killer/DR5 mRNA, which we have designated the long and short isoforms based on...

...of MCF-7 human breast cancer cells with the DNA damaging drugs adriamycin, campthothecin, or **etoposide** causes a coordinated up-regulation of both isoforms. Treatment of the p53-mutant T-47D...

...with adriamycin also results in up-regulation of both isoforms, suggesting that adriamycin up-regulates **TRAIL** -R2/Killer/DR5 expression independent of functional p53. The expression of both mRNA

isoforms are...

...in a decrease in the mRNA expression of both isoforms. These results demonstrate that the **TRAIL** -R2/Killer/DR5 gene gives rise to two distinct forms of mRNA, and that these...
...Identifiers--FADD-DEPENDENT **APOPTOSIS** ; **TRAIL** -INDUCED **APOPTOSIS** ; NF-KAPPA-B; TNF FAMILY; DEATH; RECEPTORS; IDENTIFICATION; KILLER/DR5; ACTIVATE; MEMBER

13/3,K,AB/12 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08721058 Genuine Article#: 321BH Number of References: 50
Title: Tumor necrosis factor-related apoptosis **-inducing ligand retains its** apoptosis **-inducing capacity on Bcl-2-or Bcl-x(L)-overexpressing chemotherapy-resistant tumor cells** (ABSTRACT AVAILABLE)
Author(s): Walczak H (REPRINT) ; Bouchon A; Stahl H; Krammer PH
Corporate Source: GERMAN CANC RES CTR DKFZ,TUMOR IMMUNOL PROGRAM, NEUENHEIMER FELD 280/D-69120 HEIDELBERG//GERMANY/ (REPRINT)
Journal: CANCER RESEARCH, **2000** , V60, N11 (JUN 1), P3051-3057
ISSN: 0008-5472 Publication date: 20000601
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Tumor necrosis factor-related **apoptosis** -inducing ligand (**TRAIL**) is a member of the tumor necrosis factor family and has recently been shown to exert tumoricidal activity in vivo in the absence of any observable toxicity. The signaling pathways triggered by **TRAIL** stimulation and the mechanisms involved in resistance against **TRAIL** -mediated **apoptosis** are still poorly defined. We show here that **TRAIL** -induced **apoptosis** involves late dissipation of mitochondrial membrane potential (Delta Psi(m)) and cytochrome c release. These events follow activation of caspase-8 and caspase-3 and induction of DNA fragmentation. In addition, caspase-8-deficient cells are resistant against **TRAIL** -induced **apoptosis** , and inhibition of caspase-8 but not caspase-9 prevents mitochondrial permeability transition and **apoptosis** , In contrast, various Bcl-2- or Bcl-x(L)-overexpressing tumor cell lines are sensitive to **TRAIL** -induced **apoptosis** ; however, they show a delay in **TRAIL**0 -induced mitochondrial permeability transition compared with control transfectants. This indicates that **TRAIL** -induced **apoptosis** depends on caspase-8 activation rather than on the disruption of mitochondrial integrity. Because most chemotherapeutic drugs used in the treatment of malignancies lead to **apoptosis** primarily by engagement of the mitochondrial proapoptotic machinery, we tested whether drug-resistant tumor cells retain sensitivity for **TRAIL** -induced **apoptosis** , Tumor cells overexpressing Bcl-2 or Bcl-x(L) become resistant to **apoptosis** induced by the chemotherapeutic drug **etoposide** , However, these cells are not protected or are only marginally protected against **TRAIL** -induced **apoptosis** , Thus, **TRAIL** may still kill tumors that have acquired resistance to chemotherapeutic drugs by overexpression of Bcl-2 or Bcl-x(L). These data will influence future treatment strategies involving **TRAIL** .

Title: Tumor necrosis factor-related apoptosis **-inducing ligand retains its** apoptosis **-inducing capacity on Bcl-2-or Bcl-x(L)-overexpressing chemotherapy-resistant tumor cells**
, **2000**
Abstract: Tumor necrosis factor-related **apoptosis** -inducing ligand (**TRAIL**

) is a member of the tumor necrosis factor family and has recently been shown to...

...activity in vivo in the absence of any observable toxicity. The signaling pathways triggered by **TRAIL** stimulation and the mechanisms involved in resistance against **TRAIL** -mediated **apoptosis** are still poorly defined. We show here that **TRAIL** -induced **apoptosis** involves late dissipation of mitochondrial membrane potential (Delta Psi(m)) and cytochrome c release. These...

...3 and induction of DNA fragmentation. In addition, caspase-8-deficient cells are resistant against **TRAIL** -induced **apoptosis** , and inhibition of caspase-8 but not caspase-9 prevents mitochondrial permeability transition and **apoptosis** , In contrast, various Bcl-2- or Bcl-x(L)-overexpressing tumor cell lines are sensitive to **TRAIL** -induced **apoptosis** ; however, they show a delay in **TRAIL** -induced mitochondrial permeability transition compared with control transfectants. This indicates that **TRAIL** -induced **apoptosis** depends on caspase-8 activation rather than on the disruption of mitochondrial integrity. Because most chemotherapeutic drugs used in the treatment of malignancies lead to **apoptosis** primarily by engagement of the mitochondrial proapoptotic machinery, we tested whether drug-resistant tumor cells retain sensitivity for **TRAIL** -induced **apoptosis** , Tumor cells overexpressing Bcl-2 or Bcl-x(L) become resistant to **apoptosis** induced by the chemotherapeutic drug **etoposide** , However, these cells are not protected or are only marginally protected against **TRAIL** -induced **apoptosis** , Thus, **TRAIL** may still kill tumors that have acquired resistance to chemotherapeutic drugs by overexpression of Bcl-2 or Bcl-x(L). These data will influence future treatment strategies involving **TRAIL** .

...Identifiers--CHRONIC LYMPHOCYTIC-LEUKEMIA; **TRAIL** -INDUCED **APOPTOSIS** ; CYTOCHROME-C; TUMORICIDAL ACTIVITY; RECOMBINANT

09049824 Genuine Article#: 361ER Number of References: 221
Title: Positive and negative regulation of apoptotic **pathways by cytotoxic agents in hematological malignancies** (ABSTRACT AVAILABLE)
Author(s): Solary E (REPRINT) ; Droin N; Bettaieb A; Corcos L; DimancheBoitrel MT; Garrido C
Corporate Source: INSERM U517,7 BLVD JEANNE ARC/F-21000 DIJON//FRANCE/ (REPRINT); CHU BOCAGE,CLIN HEMATOL UNIT/DIJON//FRANCE/
Journal: LEUKEMIA, **2000** , V14, N10 (OCT), P1833-1849
ISSN: 0887-6924 Publication date: 20001000
Publisher: NATURE PUBLISHING GROUP, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND
Language: English Document Type: REVIEW
Abstract: Most chemotherapeutic drugs can induce tumor cell death by **apoptosis** . Analysis of the molecular mechanisms that regulate **apoptosis** has indicated that anticancer agents simultaneously activate several pathways that either positively or negatively regulate the death process. The main pathway from specific damage induced by the drug to **apoptosis** involves activation of caspases in the cytosol by pro- **apoptotic** molecules such as cytochrome c released from the mitochondrial intermembrane space. At least in some cell types, anticancer drugs also upregulate the expression of death receptors and sensitize tumor cells to their cognate ligands. The Fas-mediated pathway could contribute to the early steps of drug-induced **apoptosis** while sensitization to the cytokine **TRAIL** could be used to amplify the response to cytotoxic drugs. The Bcl-2 family of proteins, that includes anti- and pro- **apoptotic** molecules, regulates cell sensitivity mainly at the mitochondrial level. Anticancer drugs modulate their expression leg through p53-dependent gene transcription), their activity leg by phosphorylating Bcl-2) and their subcellular localization leg by inducing the translocation of specific BH3-only pro- **apoptotic** proteins). Very early after interacting with tumor cells, anticancer drugs also activate lipid-dependent signaling pathways that either increase or decrease cell ability to die by **apoptosis** . In addition, cytotoxic agents can activate protective pathways that involve activation of NF kappa B transcription factor, accumulation of heat shock proteins such as Hsp27 and activation of proteins involved in cell cycle regulation. This review discusses how modulation of the balance between noxious and protective signals that regulate drug-induced **apoptosis** could be used to improve the efficacy of current therapeutic regimens in hematological malignancies.

Title: Positive and negative regulation of apoptotic **pathways by cytotoxic agents in hematological malignancies**
, **2000**
Abstract: Most chemotherapeutic drugs can induce tumor cell death by **apoptosis** . Analysis of the molecular mechanisms that regulate **apoptosis** has indicated that anticancer agents simultaneously activate several pathways that either positively or negatively regulate the death process. The main pathway from specific damage induced by the drug to **apoptosis** involves activation of caspases in the cytosol by pro- **apoptotic** molecules such as cytochrome c released from the mitochondrial intermembrane space. At least in some...

...cognate ligands. The Fas-mediated pathway could contribute to the early steps of drug-induced **apoptosis** while sensitization to the cytokine **TRAIL** could be used to amplify the response to cytotoxic drugs. The Bcl-2 family of proteins, that includes anti- and pro- **apoptotic**

molecules, regulates cell sensitivity mainly at the mitochondrial level. Anticancer drugs modulate their expression leg...

...2) and their subcellular localization leg by inducing the translocation of specific BH3-only pro- **apoptotic** proteins). Very early after interacting with tumor cells, anticancer drugs also activate lipid-dependent signaling pathways that either increase or decrease cell ability to die by **apoptosis** . In addition, cytotoxic agents can activate protective pathways that involve activation of NF kappa B...

...discusses how modulation of the balance between noxious and protective signals that regulate drug-induced **apoptosis** could be used to improve the efficacy of current therapeutic regimens in hematological malignancies.
...Identifiers--TUMOR-NECROSIS-FACTOR; ACUTE PROMYELOCYTIC LEUKEMIA; STRESS-INDUCED **APOPTOSIS** ; CYTOCHROME-C RELEASE; INDUCED CELL-DEATH; SIGNAL-TRANSDUCTION PATHWAY; **ETOPOSIDE** -INDUCED **APOPTOSIS** ; DEPENDENT PROTEIN-KINASE; ALPHA-INDUCED **APOPTOSIS** ; DRUG-INDUCED **APOPTOSIS**

13/3,K,AB/11 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08742919 Genuine Article#: 323VU Number of References: 25
Title: Coordinated regulation of two TRAIL **-R2/KILLER/DR5 mRNA isoforms by DNA damaging agents, serum and 17 beta-estradiol in human breast cancer cells** (ABSTRACT AVAILABLE)

Increased expression of death receptors 4 and 5 synergizes the apoptosis **response to combined treatment with** etoposide **and** TRAIL **.**

Gibson S B; Oyer R; Spalding A C; Anderson S M; Johnson G L

Program in Molecular Signal Transduction, Division of Basic Sciences, National Jewish Medical and Research Center, Denver, Colorado 80206, USA.

Molecular and cellular biology (UNITED STATES) Jan **2000** , 20 (1) p205-12, ISSN 0270-7306 Journal Code: 8109087

Contract/Grant No.: DK37871; DK; NIDDK; DK48845; DK; NIDDK; GM303024; GM; NIGMS; +

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Chemotherapeutic genotoxins induce **apoptosis** in epithelial-cell-derived cancer cells. The death receptor ligand **TRAIL** also induces **apoptosis** in epithelial-cell-derived cancer cells but generally fails to induce **apoptosis** in nontransformed cells. We show here that the treatment of four different epithelial cell lines with the topoisomerase II inhibitor **etoposide** in combination with **TRAIL** (tumor necrosis factor [TNF]-related **apoptosis** -inducing ligand) induces a synergistic **apoptotic** response. The mechanism of the synergistic effect results from the **etoposide** -mediated increase in the expression of the death receptors 4 (DR4) and 5 (DR5). Inhibition of NF-kappaB activation by expression of kinase-inactive MEK kinase 1(MEKK1) or dominant-negative IkappaB (DeltaIkappaB) blocked the increase in DR4 and DR5 expression following **etoposide** treatment. Addition of a soluble decoy DR4 fusion protein (DR4:Fc) to cell cultures reduced the amount of **etoposide** -induced **apoptosis** in a dose-dependent manner. The addition of a soluble TNF decoy receptor (TNFR:Fc) was without effect, demonstrating the specificity of DR4 binding ligands in the **etoposide** -induced **apoptosis** response. Thus, genotoxin treatment in combination with **TRAIL** is an effective inducer of epithelial-cell-derived tumor cell **apoptosis** relative to either treatment alone.

773489 PMID: 10706092

Increased death receptor 5 expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with tumor necrosis factor-related apoptosis -inducing ligand in vitro and in vivo.

Nagane M; Pan G; Weddle J J; Dixit V M; Cavenee W K; Huang H J

Ludwig Institute for Cancer Research, University of California at San Diego, La Jolla 92093-0660, USA. mnagane@ucsd.edu

Cancer research (UNITED STATES) Feb 15 **2000** , 60 (4) p847-53, ISSN 0008-5472 Journal Code: 2984705R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The intractability of malignant gliomas to multimodality treatments plays a large part in their extremely poor prognosis. Tumor necrosis factor-related **apoptosis** -inducing ligand (**TRAIL**) is a novel member of the tumor necrosis factor (TNF) family that induces **apoptosis** preferentially in tumor cells through binding to its cognate death receptors, DR4 and DR5. Here we show that the DNA-damaging chemotherapeutic drugs, cis-diamminedichloroplatinum(II) (CDDP) and **etoposide** , elicited increased expression of DR5 in human glioma cells. Exposure of such cells in vitro to soluble human **TRAIL** in combination with CDDP or **etoposide** resulted in synergistic cell death that could be blocked by soluble **TRAIL** -neutralizing DR5-Fc or the caspase inhibitors, Z-Asp-CH2-DCB and CrmA. Moreover, systemic in vivo administration of **TRAIL** with CDDP synergistically suppressed both tumor formation and growth of established s.c. human glioblastoma xenografts in nude mice by inducing **apoptosis** without causing significant general toxicity. The combination treatment resulted in complete and durable remission in 29% of mice with the established s.c. xenografts and also significantly extended the survival of mice bearing intracerebral xenografts. These results provide preclinical proof-of-principle for a novel therapeutic strategy in which the death ligand, **TRAIL** , is safely combined with conventional DNA-damaging chemotherapy.

... expression by chemotherapeutic agents in human gliomas causes synergistic cytotoxicity with tumor necrosis factor-related apoptosis **-inducing ligand in vitro and in vivo.**

Feb 15 **2000** ,

... multimodality treatments plays a large part in their extremely poor prognosis. Tumor necrosis factor-related **apoptosis** -inducing ligand (**TRAIL**) is a novel member of the tumor necrosis factor (TNF) family that induces **apoptosis** preferentially in tumor cells through binding to its cognate death receptors, DR4 and DR5. Here we show that the DNA-damaging chemotherapeutic drugs, cis-diamminedichloroplatinum(II) (CDDP) and **etoposide** , elicited increased expression of DR5 in human glioma cells. Exposure of such cells in vitro to soluble human **TRAIL** in combination with CDDP or **etoposide** resulted in synergistic cell death that could be blocked by soluble **TRAIL** -neutralizing DR5-Fc or the caspase inhibitors, Z-Asp-CH2-DCB and CrmA. Moreover, systemic in vivo administration of **TRAIL** with CDDP synergistically suppressed both tumor formation and growth of established s.c. human glioblastoma xenografts in nude mice by inducing **apoptosis** without causing significant general toxicity. The combination treatment resulted in complete and durable remission in...

... provide preclinical proof-of-principle for a novel therapeutic strategy in which the death ligand, **TRAIL** , is safely combined with conventional DNA-damaging chemotherapy.

Chemical Name: Antineoplastic Agents; Membrane Glycoproteins

5/3,K,AB/11 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05523321 Genuine Article#: WE076 Number of References: 23
Title: Adriamycin **induces apoptosis in rat thymocytes** (ABSTRACT AVAILABLE)
Author(s): Azmi S; Bhatia L; Khanna N; Dhawan D; Singh N (REPRINT)
Corporate Source: ALL INDIA INST MED SCI,DEPT BIOCHEM, ANSARI NAGAR/NEW DELHI 110029//INDIA/ (REPRINT); ALL INDIA INST MED SCI,DEPT BIOCHEM/NEW DELHI 110029//INDIA/
Journal: CANCER LETTERS, **1997** , V111, N1-2 (JAN 1), P225-231
ISSN: 0304-3835 Publication date: 19970101
Publisher: ELSEVIER SCI IRELAND LTD, CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND
Language: English Document Type: ARTICLE
Abstract: Apoptosis is a controlled form of cell death accompanied by distinct morphological and biochemical changes. In this study the nature of cytotoxicity induced by **adriamycin** (ADM) in rat thymocytes was evaluated. Morphological and biochemical changes characteristic of apoptosis were found to precede **adriamycin** -induced cell death. Our findings demonstrate the involvement of c-Myc, c-Jun, antioxidant enzymes CuZn superoxide dismutase and catalase, and perhaps poly ADP ribosylation in ADM-induced cell death. (C) 1997 Elsevier Science Ireland Ltd.
Title: Adriamycin **induces apoptosis in rat thymocytes**
, **1997**
...Abstract: by distinct morphological and biochemical changes. In this study the nature of cytotoxicity induced by **adriamycin** (ADM) in rat thymocytes was evaluated. Morphological and biochemical changes characteristic of apoptosis were found to precede **adriamycin** -induced cell death. Our findings demonstrate the involvement of c-Myc, c-Jun, antioxidant enzymes...

Apoptosis **of human tumor cells by** chemotherapeutic **anthracyclines is enhanced by Bax overexpression** (ABSTRACT AVAILABLE)

Author(s): Lu YJ; Yagi T (REPRINT)
Corporate Source: KYOTO UNIV,GRAD SCH MED, DEPT RADIAT GENET, SAKYO KU, YOSHIDA KONOE CHO/KYOTO 6068501//JAPAN/ (REPRINT); KYOTO UNIV,GRAD SCH MED, DEPT RADIAT GENET, SAKYO KU/KYOTO 6068501//JAPAN/

Journal: JOURNAL OF RADIATION RESEARCH, **1999** , V40, N3 (SEP), P263-272
ISSN: 0449-3060 Publication date: 19990900
Publisher: JAPAN RADIATION RESEARCH SOC, C/O NAT INST RADIOLOGICAL SCI 9-1 ANAGAWA-4-CHOME INAGE-KU, CHIBA 263, JAPAN
Language: English Document Type: ARTICLE

Abstract: One of the major factors for efficacy of a chemotherapeutic drug is its activity to induce apoptosis of tumor cells. Doxorubicin and daunorubicin, radiomimetic anthracycline-group drugs, have been used for chemotherapy for about 30 years. Here we established the colorectal tumor and osteosarcoma cells in which Bar expression can be induced by the treatment of isopropyl-beta-D-thiogalactopyranoside, and examined the effect of the Bar overexpression on the cell death caused by these drugs. While the Bar overexpression neither affected growth nor morphology of the undamaged cells, it enhanced the cell death caused by these drugs. Increase in cellular nucleus fragmentation and DNA ladder formation indicates that the Bar-enhanced cell death is due to enhanced apoptosis of the drug-treated cells. The enhanced cell death was nor observed when the cells were irradiated with X-ray or treated with other chemotherapeutic agents we examined. These results indicate that Bar may have a specific role to enhance the efficacy of chemothrapy with anthracycline-group agents.

Title: Apoptosis **of human tumor cells by** chemotherapeutic **anthracyclines is enhanced by Bax overexpression**

Enhancement of chemotherapeutic **agents induced-** apoptosis **associated with activation of c-Jun N-terminal kinase 1 and caspase 3 (CPP32) in bax-transfected gastric cancer cells.**

Kim R; Ohi Y; Inoue H; Toge T
Department of Surgical Oncology, Hiroshima University, Japan.

Anticancer research (GREECE) Jan-Feb **2000** , 20 (1A) p439-44, ISSN 0250-7005 Journal Code: 8102988
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Apoptois is an important determinant in the sensitivity to chemotherapeutic agents in gastric cancer cells. In this study, we examined whether the introduction of the bax gene into MKN45 gastric cancer cells could enhance the sensitivity to **chemotherapeutic** agents in association with **apoptosis** . **Apoptosis** in the bax-transfected gastric cancer cells was enhanced following the treatment of various chemotherapeutic agents including **adriamycin** (ADM), cisplatin (CDDP), etoposide (VP-16) and taxotere (TXT) as compared to those of neo gene-transfected cells. The enhancement of apoptosis was coincident with the increase of sensitivity in the ratio of IC50 value, that was 1.3-fold in ADM, 4.4-fold in CDDP, 4.6-fold in VP-16 and 2.5-fold in TXT, respectively. Further, the enhancement of apoptosis in the bax-transfected gastric cancer cells was associated with the activation of c-Jun N-terminal kinase 1 (JNK 1) and caspase 3 (CPP32). The increases of sensitivities to these agents in the bax-transfected cells were also demonstrated in in vivo experiments using the tumor cells transplanted into nude mice. The tumor growth in the bax-transfected cells was significantly suppressed following the treatment of CDDP or VP-16 compared to that of neo-transfected cells ($p < 0.05$). These results indicated that, the bax gene might play a critical role in determination of sensitivity to chemotherapeutic agent in gastric cancer cells in vivo, and that the activation of JNK 1 and CPP32 might be involved in the signal transduction pathways leading to apoptosis.

```
? S MIFEPRISTONE
      S1     7114  MIFEPRISTONE
? S (DEATH(W)RECEPTOR) OR DR4 OR DR5
          672679  DEATH
         1851883  RECEPTOR
            4863  DEATH(W)RECEPTOR
            8703  DR4
            2905  DR5
      S2    14497  (DEATH(W)RECEPTOR) OR DR4 OR DR5
? S S1 AND S2
            7114  S1
           14497  S2
      S3        9  S1 AND S2
? RD
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S4        8  RD (unique items)
? T S4/3,K,AB/1-8

 4/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2005 Dialog. All rts. reserv.

16562912   PMID: 15590983
  Effects of glucocorticoids on Fas gene expression in bovine blood
neutrophils.
  Chang Ling-Chu; Madsen Sally A; Toelboell Trine; Weber Patty S D; Burton
Jeanne L
  Immunogenetics Laboratory, Department of Animal Science, Michigan State
University, East Lansing, MI 48824, USA.
  Journal of endocrinology (England) Dec 2004, 183 (3) p569-83, ISSN
0022-0795 Journal Code: 0375363
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  Blood neutrophils are extremely short-lived cells that are programmed for
rapid apoptosis after differentiation in bone marrow. Recently,
glucocorticoids have been shown to prolong survival of human and rodent
neutrophils, but the mechanisms and implications for leukocyte homeostasis
and health are unclear. In this study, we investigated the effects of
endogenous and exogenous glucocorticoids on Fas expression in bovine
neutrophils because Fas is a major death receptor that stimulates
apoptosis in circulating cells. Our study subjects were four periparturient
dairy cows whose blood concentrations of cortisol peaked at calving, 15
dexamethasone-treated steers and three untreated steers whose neutrophils
were exposed to dexamethasone in vitro. Fas mRNA abundance changes in
collected neutrophils were monitored numerous times relative to the in vivo
glucocorticoid challenges, and the relationships between these data and
circulating neutrophil counts were estimated by correlation analyses. Fas
mRNA and protein abundance, caspase 8 activity, and survival of neutrophils
in vitro were also monitored in the presence and absence of dexamethasone.
In the periparturient cows, Fas mRNA abundance in circulating neutrophils
showed a sharp decrease between calving and 12 h postpartum. Based on PROC
CORR analysis (SAS), this correlated negatively with blood neutrophil count
(r=-0.634; P=0.0009) and serum cortisol concentration (r=-0.659; P<0.0001),
but showed no relationship with serum progesterone or estradiol
concentrations (P > or =0.09). Administration of dexamethasone to steers
```

also caused a pronounced reduction in neutrophil Fas mRNA abundance that persisted for 12 h and correlated negatively with blood neutrophil count (r=-0.748; P=0.0021). In vitro, dexamethasone caused dose-dependent loss of GR proteins from the cytosol of neutrophils concurrently with Fas mRNA downregulation, which was inhibited by the glucocorticoid receptor (GR) antagonist, RU486. Dexamethasone treatment of cultured neutrophils also reduced surface Fas expression, spontaneous and sFasL-induced caspase 8 activity, and rate of apoptosis in the cells. Taken together, these in vivo and in vitro results suggest that glucocorticoids inhibit Fas expression in bovine blood neutrophils via GR activation, possibly contributing to the cells' increased longevity in culture and the pronounced neutrophilia observed in parturient cows and hormone-treated steers. We thus conclude that glucocorticoid-activated GR may change the homeostasis of circulating neutrophils, in part through its negative effects on Fas gene expression and downstream apoptosis signaling pathways.

... endogenous and exogenous glucocorticoids on Fas expression in bovine neutrophils because Fas is a major **death receptor** that stimulates apoptosis in circulating cells. Our study subjects were four periparturient dairy cows whose...

...; metabolism--ME; Cattle; Cells, Cultured; Gene Expression--drug effects--DE; Hydrocortisone--blood--BL; Leukocyte Count; **Mifepristone** --pharmacology--PD; Pregnancy; RNA, Messenger--analysis--AN; Receptors, Glucocorticoid--antagonists and inhibitors--AI; Receptors, Glucocorticoid ...

Chemical Name: Antigens, CD95; Glucocorticoids; RNA, Messenger; Receptors, Glucocorticoid; Dexamethasone; Hydrocortisone; **Mifepristone** ; Caspases; caspase 8

4/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14836182 PMID: 12810637

Glucocorticoid cotreatment induces apoptosis resistance toward cancer therapy in carcinomas.

Herr Ingrid; Ucur Esat; Herzer Kerstin; Okouoyo Stella; Ridder Rudiger; Krammer Peter H; von Knebel Doeberitz Magnus; Debatin Klaus-Michael

Division of Molecular Oncology/Pediatrics, German Cancer Research Center, 69120 Heidelberg, Germany. i.herr@dkfz.de

Cancer research (United States) Jun 15 2003, 63 (12) p3112-20, ISSN 0008-5472 Journal Code: 2984705R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Chemotherapy and radiation therapy for cancer often have severe side effects that limit their efficacy. Glucocorticoids (GCs) are frequently used as cotreatment because they may have potent proapoptotic properties and reduce nausea, hyperemesis, and acute toxicity on normal tissue. In contrast to the proapoptotic effect of GCs in lymphoid cells, resistance toward cancer therapy-mediated apoptosis was induced in solid tumors of human cervix and lung carcinomas. Filter hybridization, expression data, as well as functional assays identified multiple core apoptosis molecules, which are regulated by GCs in a pro- or antiapoptotic manner. Both antiapoptotic genes such as FLIP and members of the Bcl-2 and IAP family as well as proapoptotic elements of the **death receptor** and mitochondrial apoptosis pathways were down-regulated in carcinomas resulting in a decreased activity of caspase-8, caspase-9, and caspase-3. In contrast,

death receptor and mitochondrial apoptosis signaling as well as caspase activity was enhanced by dexamethasone in lymphoid cells. To restore apoptosis sensitivity in dexamethasone-treated carcinomas, caspase-8 and caspase-9 were transfected. This resensitized tumor cells in vitro and xenografts in vivo to cisplatin induced cell death. These data therefore raise concern about the widespread combined use of GCs with antineoplastic drugs or agents in the clinical management of cancer patients.

... members of the Bcl-2 and IAP family as well as proapoptotic elements of the **death receptor** and mitochondrial apoptosis pathways were down-regulated in carcinomas resulting in a decreased activity of caspase-8, caspase-9, and caspase-3. In contrast, **death receptor** and mitochondrial apoptosis signaling as well as caspase activity was enhanced by dexamethasone in lymphoid...

...Descriptors: Proteins; *Cisplatin--pharmacology--PD; *Dexamethasone --pharmacology--PD; *Drug Resistance, Neoplasm; *Intracellular Signaling Peptides and Proteins; * **Mifepristone** --pharmacology--PD...; drug effects --DE; Humans; Lung Neoplasms--pathology--PA; Membrane Glycoproteins --pharmacology--PD; Mice; Mice, Nude; **Mifepristone** --therapeutic use--TU; Mitochondria--physiology--PH; Neoplasm Proteins--biosynthesis--BI; Neoplasm Proteins--genetics--GE; Proto...

...Chemical Name: Necrosis Factor; Recombinant Proteins; TNF-related apoptosis-inducing ligand; Tumor Necrosis Factor-alpha; Cisplatin; Dexamethasone; **Mifepristone** ; Fad7 protein, Arabidopsis; Fatty Acid Desaturases; Caspases; caspase 8; caspase 9

4/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13898466 PMID: 11585752
Differential expression of members of the tumor necrosis factor alpha-related apoptosis-inducing ligand pathway in prostate cancer cells.
Sridhar S; Ali A A; Liang Y; El Etreby M F; Lewis R W; Kumar M V
Medical College of Georgia, Section of Urology, Augusta, Georgia 30912, USA.
Cancer research (United States) Oct 1 2001, 61 (19) p7179-83, ISSN 0008-5472 Journal Code: 2984705R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Androgen ablation therapy induces apoptosis only in androgen-sensitive prostate cancer cells; therefore, other cytotoxic drugs are being used to induce apoptosis in androgen-refractory cells. **Mifepristone** , an antiprogestin used individually or together with the antiestrogen Tamoxifen, has been recommended for induction of cell death and treatment of several hormonal cancers. However, little is known about the mechanism of action of these drugs in prostate cancer. Therefore, we investigated the effect of **Mifepristone** on the tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL) pathway, a newly identified and very effective member of tumor necrosis factor-alpha family. **Mifepristone** and Tamoxifen induced significant expression of death receptors in prostate cancer cells in vitro and in xenografts. However, **Mifepristone** in combination with Tamoxifen did not increase prostate cancer cell death compared with their individual values. The involvement of the TRAIL pathway was further confirmed by the activation of caspase-8 in **Mifepristone** -treated cells. This was followed by truncation of Bid, confirming that

Mifepristone activates the TRAIL pathway. This knowledge is being used to design a combination treatment of TRAIL and **Mifepristone** to induce significant apoptosis in prostate cancer cells.

... cells; therefore, other cytotoxic drugs are being used to induce apoptosis in androgen-refractory cells. **Mifepristone** , an antiprogestin used individually or together with the antiestrogen Tamoxifen, has been recommended for induction...

... mechanism of action of these drugs in prostate cancer. Therefore, we investigated the effect of **Mifepristone** on the tumor necrosis factor alpha-related apoptosis-inducing ligand (TRAIL) pathway, a newly identified and very effective member of tumor necrosis factor-alpha family. **Mifepristone** and Tamoxifen induced significant expression of death receptors in prostate cancer cells in vitro and in xenografts. However, **Mifepristone** in combination with Tamoxifen did not increase prostate cancer cell death compared with their individual...

...involvement of the TRAIL pathway was further confirmed by the activation of caspase-8 in **Mifepristone** -treated cells. This was followed by truncation of Bid, confirming that **Mifepristone** activates the TRAIL pathway. This knowledge is being used to design a combination treatment of TRAIL and **Mifepristone** to induce significant apoptosis in prostate cancer cells.

...; Protocols--pharmacology--PD; Apoptosis--drug effects--DE; Humans; Mice; Mice, Inbred BALB C; Mice, Nude; **Mifepristone** --pharmacology--PD; Prostatic Neoplasms--pathology--PA; Signal Transduction--drug effects--DE; Signal Transduction--physiology--PH...

...Chemical Name: Membrane Glycoproteins; Receptors, Tumor Necrosis Factor; TNF-related apoptosis-inducing ligand; Tumor Necrosis Factor-alpha; **death receptor** -4; **death receptor** -5; Tamoxifen; **Mifepristone**

4/3,K,AB/4 (Item 4 from file: 155)

13564680 PMID: 11145719

Role of the CD95/CD95 ligand system in glucocorticoid-induced monocyte apoptosis.

Schmidt M; Lugering N; Lugering A; Pauels H G; Schulze-Osthoff K; Domschke W; Kucharzik T

Departments of Medicine B and Immunology and Cell Biology, Institute for Immunology, University of Munster, Munster, Germany.

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jan 15 2001, 166 (2) p1344-51, ISSN 0022-1767 Journal Code: 2985117R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Glucocorticoids (GC) act as potent anti-inflammatory and immunosuppressive agents on a variety of immune cells. However, the exact mechanisms of their action are still unknown. Recently, we demonstrated that GC induce apoptosis in human peripheral blood monocytes. In the present study, we examined the signaling pathway in GC-induced apoptosis. Monocyte apoptosis was demonstrated by annexin V staining, DNA laddering, and electron microscopy. Apoptosis required the activation of caspases, as different caspase inhibitors prevented GC-induced cell death. In addition, the proteolytic activation of caspase-8 and caspase-3 was observed. In

additional experiments, we determined the role of the **death receptor** CD95 in GC-induced apoptosis. CD95 and CD95 ligand (CD95L) were up-regulated in a dose- and time-dependent manner on the cell membrane and also released after treatment with GC. Costimulation with the GC receptor antagonist **mifepristone** diminished monocyte apoptosis as well as CD95/CD95L expression and subsequent caspase-8 and caspase-3 activation. In contrast, the caspase inhibitor N:-acetyl-Asp-Glu-Val-Asp-aldehyde suppressed caspase-3 activation and apoptosis, but did not down-regulate caspase-8 activation and expression of CD95 and CD95L. Importantly, GC-induced monocyte apoptosis was strongly abolished by a neutralizing CD95L mAb. Therefore, our data suggest that GC-induced monocyte apoptosis is at least partially mediated by an autocrine or paracrine pathway involving the CD95/CD95L system.

...8 and caspase-3 was observed. In additional experiments, we determined the role of the **death receptor** CD95 in GC-induced apoptosis. CD95 and CD95 ligand (CD95L) were up-regulated in a...

... cell membrane and also released after treatment with GC. Costimulation with the GC receptor antagonist **mifepristone** diminished monocyte apoptosis as well as CD95/CD95L expression and subsequent caspase-8 and caspase...

4/3,K,AB/5 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0013961046 BIOSIS NO.: 200200554557
Induction of apoptosis as a treatment option for prostate cancer
AUTHOR: Kumar M V (Reprint); Eid M A (Reprint); Liang Y (Reprint); Lewis R W (Reprint)
AUTHOR ADDRESS: Section of Urology, Medical College of Georgia, Augusta, GA, USA**USA
JOURNAL: International Journal of Cancer Supplement (13): p341 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 18th UICC International Cancer Congress Oslo, Norway June 30-July 05, 2002; 20020630
ISSN: 0898-6924
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

...REGISTRY NUMBERS: **mifepristone**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **death receptor** -4 { **DR4** }--...

... **death receptor** -5 { **DR5** }--...
... **mifepristone** --

4/3,K,AB/6 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0013815636 BIOSIS NO.: 200200409147
Pre-treatment with mifepristone **sensitizes resistant prostate cancer cells to TRAIL**
AUTHOR: Eid Manal A (Reprint); Lewis Ronald W (Reprint); Kumar M Vijay (Reprint)

AUTHOR ADDRESS: Medical College of Georgia, Augusta, GA, USA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p579 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Pre-treatment with mifepristone **sensitizes resistant prostate cancer cells to TRAIL**
...REGISTRY NUMBERS: **mifepristone**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **death receptor** --...

... **mifepristone** --

4/3,K,AB/7 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02385125 Genuine Article#: KY849 Number of References: 39
Title: GLUCOCORTICOID-MEDIATED CONTROL OF THE ACTIVATION AND CLONAL DELETION OF PERIPHERAL T-CELLS INVIVO (Abstract Available)
Author(s): GONZALO JA; GONZALEZGARCIA A; MARTINEZA C; KROEMER G
Corporate Source: UNIV AUTONOMA MADRID,CSIC,CTR BIOL MOLEC,CAMPUSCANTOBLANCO/E-28049 MADRID//SPAIN/; UNIV AUTONOMA MADRID,CSIC,CTR BIOL MOLEC,CAMPUSCANTOBLANCO/E-28049 MADRID//SPAIN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1993, V177, N5 (MAY 1), P 1239-1246
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE
Abstract: Poly- and oligoclonal T cell stimuli like anti-CD3epsilon monoclonal antibody or Staphylococcus aureus enterotoxin B (SEB), injected at doses that per se are not lethal, provoke acute death within less than 24 h, provided that endogenous glucocorticoids (GC) are depleted by adrenalectomy or by injection of saturating amounts of the GC receptor antagonist RU-38486 (**mifepristone**). Pharmacological doses of the GC agonist dexamethasone (DEX) alter the in vivo response of splenic Vbeta8+ T cells to SEB, thus impeding the expansion of such cells and causing their rapid (3 d) clonal deletion. In contrast, coadministration of RU-38486 counteracts a SEB-induced early (12 h) reduction of Vbeta8+CD4+ and Vbeta8+CD8+ spleen cells. In vivo T cell stimulation by injection of bacterial superantigen induces a rapid (peak at 90-120 min) increase in corticosterone serum levels, suggesting that endogenous GC might control early T cell activation. Accordingly, kinetic studies revealed that RU-38486 has to be administered within 2 h after superantigen administration to exert its lethal effect. Similarly, exogenous GC must be injected during this critical phase (2 h) to rescue animals from acute death induced by coinjection of SEB and D-galactosamine (GaIN). Adrenalectomy, injection of RU-38486 and priming with GaIN per se provoke the programmed death of peripheral CD4+ and CD8+ T cells. Thus, three manipulations that sensitize mice for the lethal effect of T cell stimulation also exert a proapoptotic effect on peripheral T cells. In synthesis, endogenous and exogenous GC regulate T cell responses and determine the propensity of

peripheral T cells to undergo apoptosis.

...Abstract: by adrenalectomy or by injection of saturating amounts of the GC receptor antagonist RU-38486 (**mifepristone**). Pharmacological doses of the GC agonist dexamethasone (DEX) alter the in vivo response of splenic...
...Identifiers--STAPHYLOCOCCAL ENTEROTOXIN-B; PITUITARY-ADRENAL AXIS; TUMOR-NECROSIS-FACTOR; MONOCLONAL-ANTIBODY; IMMUNE-SYSTEM; MICE; **DEATH; RECEPTOR;** BETA; INTERLEUKIN-2
...Research Fronts: RELEASE OF RAT CORTICOTROPIN-RELEASING FACTOR (CRF); PITUITARY-ADRENAL AXIS; BRAIN MACROPHAGES)
91-2026 001 (**MIFEPRISTONE** (RU-486); PROGESTERONE ANTAGONISTS; UTERINE ACTIVITY; ANTIPROGESTIN RU486; PREGNANT RHESUS-MONKEY)
91-2211 001 (T...

4/3,K,AB/8 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 10171921 IFI Acc No: 2002-0115613
IFI Publication Control No: 2002-0115613 IFI Chemical Acc No: 2002-0029792
Document Type: C
TREATMENT OF PROSTATE CANCER; INDUCING CELL DEATH BY TREATING WITH TUMOR NECROSIS FACTOR ALPHA-RELATED APOPTOSIS INDUCING LIGAND (TRAIL) AND, OPTIONALLY AN ANTIPROGESTIN, E.G., MIFEPRISTONE
Inventors: Kumar M Vijay (US)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000
Publication (No,Kind,Date), Applic (No,Date):
US 20020115613 A1 20020822 US 200277435 20020215
Priority Applic(No,Date): US 200277435 20020215
Provisional Applic(No,Date): US 60-269698 20010216

Abstract: The present invention provides methods and compositions for treating cancer, and even more preferably, prostate cancer. In one aspect, the present invention comprises a method for inducing cell death in cancer cells comprising treating at least a portion of the cancer cells with an effective amount of TRAIL and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a portion of the treated cancer cells. In another aspect, the present invention comprises a composition for treating cancer by inducing cell death in cancer cells comprising a pharmaceutical composition comprising an effective amount of TRAIL and an effective amount of an antiprogestin sufficient to induce apoptosis in at least a portion of the cancer cells exposed to the composition. In an embodiment, the antiprogestin is **Mifepristone** .

...TUMOR NECROSIS FACTOR ALPHA-RELATED APOPTOSIS INDUCING LIGAND (TRAIL) AND, OPTIONALLY AN ANTIPROGESTIN, E.G., MIFEPRISTONE

Abstract: ...portion of the cancer cells exposed to the composition. In an embodiment, the antiprogestin is **Mifepristone** .
Non-exemplary Claims: ...3. The method of claim 2, wherein the antiprogestin comprises **Mifepristone** .
...

...with a pharmaceutical composition comprising an effective amount of TRAIL and an effective amount of **Mifepristone** sufficient to induce apoptosis in at least a portion of the treated cancer cells...

...5. The method of claim 4, wherein the cancer cells are treated with **Mifepristone** prior to being treated with TRAIL...
...6. The method of claim 4, wherein the cancer cells are treated with **Mifepristone** and TRAIL concurrently...

...10. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 1,000 mu M...

...11. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 100 mu M...

...12. The method of claim 4, wherein the dose of **Mifepristone** in said pharmaceutical composition results in a local concentration of **Mifepristone** at the tumor which ranges from 5 to 20 mu M...16. The method of claim 4, wherein the treatment of cancer cells with TRAIL and **Mifepristone** is associated with an increase in at least one **death receptor** in at least a portion of the treated cells...

...17. The method of claim 16, further comprising an increase in the **death receptor** **DR4** and/or **DR5** .
...
...18. The method of claim 4, wherein the treatment of cancer cells with TRAIL and **Mifepristone** is associated with an increase in activated caspase enzymes...

...20. The method of claim 4, wherein the treatment of cancer cells with TRAIL and **Mifepristone** is associated with an increase in truncated BID protein (tBid) in at least a portion...

...21. The method of claim 4, wherein the treatment of cancer cells with TRAIL and **Mifepristone** is associated with a reduction in mitochondrial function...

...22. The method of claim 4, wherein the treatment of cancer cells with TRAIL and **Mifepristone** results in an increase in apoptosome formation in at least a portion of the treated...29. The composition of claim 28, wherein the antiprogestin comprises **Mifepristone** .
...

...cancer by inducing cell death in cancer cells comprising an effective amount of TRAIL and **Mifepristone** in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL and **Mifepristone** to induce apoptosis in at least a portion of said cancer cells exposed to said...

...31. The composition of claim 30, wherein said **Mifepristone** and said TRAIL are packaged in such a manner that said **Mifepristone** is at least partially released for application to the cancer prior to the release of ...

...32. The composition of claim 30, wherein said **Mifepristone** and said TRAIL are packaged in such a manner so as to be released substantially ...

...36. The composition of claim 30, wherein the dose of 1Mifepristone results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 1,000 mu M...

...37. The composition of claim 30, wherein the dose of **Mifepristone** results in a local concentration of **Mifepristone** at the tumor which ranges from 1 to 100 mu M...

...38. The composition of claim 30, wherein the dose of **Mifepristone** results in a local concentration of **Mifepristone** at the tumor which ranges from 5 to 20 mu M...43. The kit of claim 42, wherein said antiprogestin comprises **Mifepristone** .

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? S ADRIAMYCIN
      S1     622  ADRIAMYCIN
? S APOPTOSIS
      S2    3483  APOPTOSIS
? S S1 AND S2
             622  S1
            3483  S2
      S3      47  S1 AND S2
? S S3 AND PY<2001
              47  S3
         3480039  PY<2001
      S4       5  S3 AND PY<2001
? T S4/3,K,AB/1-5
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4/3,K,AB/1

DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 04041704
IFI Chemical Acc No: 2004-0010472
Document Type: C

COMBINED PREPARATION FOR THE TREATMENT OF NEOPLASIC DISEASES OR OF INFECTIOUS DISEASES; MONOCYTE DERIVED CELLS, PARTICULARLY CYTOTOXIC MACROPHAGES, CHEMOTHERAPY OR IMMUNOTHERAPY DRUGS, FOR THE SIMULTANEOUS, SEPARATE OR SEQUENTIAL USE, FOR THE TREATMENT OF CANCER OR INFECTIOUS DISEASES.

Inventors: Bartholeyns Jacques (FR); Fouron Yves (US); Romet-Lemonne Jean-Loup (FR)
Assignee: IDM Immuno-Designed Molecules FR
Assignee Code: 40775

Publication (No,Kind,Date), Applic (No,Date):
US 6713056 B1 20040330 US 2000647529 20001129
Internat. Convention Pub(No,Date),Applic(No,Date): WO 9951248
19991014 WO 99EP2105 19990329
Section 371: 20001129
Section 102(e):20001129
Priority Applic(No,Date): EP 98400783 19980402

Abstract: The present invention relates to combined preparation containing as active substance the following individual components, in the form of a kit-of-parts: monocyte derived cells, particularly cytotoxic macrophages, chemotherapy or immunotherapy drugs, for the simultaneous, separate or sequential use, for the treatment of cancer or infectious diseases.

...Internat. Convention Pub(No,Date),Applic(No,Date): **19991014**
Non-exemplary Claims: ...wherein the chemotherapy drug is selected from the group of compounds consisting of anthracyclins, daunorubicin, **adriamycin** , taxoter derivatives, vinca alcaloids, vincristine, taxol, carmustine, cisplatin, fluorouracils, polyamine inhibitors, topoisomerase inhibitors, tamoxifene, prodasone...

...said drug is selected from the group consisting of cytotoxic compounds, cytostatic compounds, compounds inducing **apoptosis** or cytokines, said drug administered at a dose of 0.1 to 100 mg/day...

4/3,K,AB/2

DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3330439 IFI Acc No: 0016549
IFI Publication Control No: 0016549
Document Type: C
METHODS AND COMPOSITIONS COMPRISING DNA DAMAGING AGENTS AND P53; KILLING TUMOR, CANCER CELLS; ENHANCED SENSITIVITY TO THERAPYUSING POLYNUCLEOTIDE
Inventors: Fujiwara Toshiyoshi (JP); Grimm Elizabeth A (US); Mukhopadhyay Tapas (US); Owen-Schaub Laurie B (US); Roth Jack A (US); Zhang Wei-Wei (US)
Assignee: Texas, University of System
Assignee Code: 83960
Publication (No,Kind,Date), Applic (No,Date):
US 6069134 A **20000530** US 97953290 19971017
Calculated Expiration: 20110306
(Cited in 001 later patents)
Document Type: CERTIFICATE OF CORRECTION
Certificate of Correction Date: 20010417
Priority Applic(No,Date): US 97953290 19971017; US 91665538 19910306; US 92960543 19921013; US 93145826 19931029; US 94233002 19940425

Abstract: The present invention relates to the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells. A tumor suppressor gene, p53, was delivered via a recombinant adenovirusmediated gene transfer both in vitro and in vivo, in combination with a chemotherapeutic agent. Treated cells underwent **apoptosis** with specific DNA fragmentation. Direct injection of the p53adenovirus construct into tumors subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors. The invention also provides for the clinical application of a regimen combining gene replacement using replication-deficient wild-type p53 adenovirus and DNA-damaging drugs for treatment of human cancer.

Publication (No,Kind,Date), Applic (No,Date):
... **20000530**

Abstract: ...both in vitro and in vivo, in combination with a chemotherapeutic agent. Treated cells underwent **apoptosis** with specific DNA fragmentation. Direct injection of the p53adenovirus construct into tumors subcutaneously, followed by...
Non-exemplary Claims: ...66. The method of claim 14, wherein said chemotherapeutic is **adriamycin** .

4/3,K,AB/3
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3313061 IFI Acc No: 0012450
IFI Publication Control No: 0012450
Document Type: C
SUPPLEMENTED AND UNSUPPLEMENTED TISSUE SEALANTS, METHODS OF THEIR PRODUCTION AND USE; A FOAMABLE FIBRIN MATRIX COMPRISING FIBRINOGEN OR METABOLITE AND AN FOAMING AGENT WHICH CAUSES FIBRINOGEN TO FOAM DURING APPLICATION OF FIBRINOGEN TO WOUNDED TISSUE
Inventors: Drohan William Nash (US); MacPhee Martin James (US); Woolverton Christoper J (US)
Assignee: American National Red Cross

Assignee Code: 03914
Publication (No,Kind,Date), Applic (No,Date):
US 6054122 A **20000425** US 95479034 19950607
Calculated Expiration: 20170425
(Cited in 006 later patents) **Document Type: REISSUE REQUESTED**
Priority Applic(No,Date): US 95479034 19950607; US 9331164 19930312; US 90618419 19901127; US 91798919 19911127; US 94328552 19941025; US 94351006 19941207

Abstract: This invention provides a fibrin sealant dressing, wherein said fibrin sealant may be supplemented with at least one composition selected from, for example, one or more regulatory compounds, antibody, antimicrobial compositions, analgesics, anticoagulants, antiproliferatives, anti-inflammatory compounds, cytokines, cytotoxins, drugs, growth factors, interferons, hormones, lipids, demineralized bone or bone morphogenetic proteins, cartilage inducing factors, oligonucleotides polymers, polysaccharides, polypeptides, protease inhibitors, vasoconstrictors or vasodilators, vitamins, minerals, stabilizers and the like. Also disclosed are methods of preparing and/or using the unsupplemented or supplemented fibrin sealant dressing.

Publication (No,Kind,Date), Applic (No,Date):
... **20000425**
Non-exemplary Claims: ...membrane permeability modifiers, DNA intercalators, metabolites, dichloroethylsulfide derivatives, protein production inhibitors, ribosome inhibitors, inducers of **apoptosis** , and neurotoxins...

...cell proliferation inhibiting compound is selected from the group consisting of 5-fluorouracil, actinomycin D, **adriamycin** , azaribine, bleomycin, busulfan, carmustine, chlorambucil, cisplatin, cytarabine, dacarbazine, estrogen, hormone analogs, insulins, hydoxyurea, L-asparaginase...

4/3,K,AB/4
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3300044 IFI Acc No: 0009337
IFI Publication Control No: 0009337
Document Type: C
METHOD FOR INDUCING APOPTOSIS **OF PRIMARY CENTRAL NERVOUS SYSTEM B CELL LYMPHOMAS; ADMINISTERING INTRATHECALLY OR INTRALESIONALLY A THERAPEUTICALLY EFFECTIVE AMOUNT OF A FAS-CROSSLINKING COMPONENT SELECTED FROM AN AGONSIT ANTIHUMAN FAS MONOCLONAL ANTIBODY, ANTI-HUMAN FAS BID FRAGMENTS, OR SOLUBLE FAS-LIGAND**
Inventors: Baiocchi Robert B (US); Caligiuri Michael A (US)
Assignee: Health Research Inc
Assignee Code: 11684
Publication (No,Kind,Date), Applic (No,Date):
US 6042826 A **20000328** US 97969881 19971114
Calculated Expiration: 20171114
(Cited in 001 later patents)
Priority Applic(No,Date): US 97969881 19971114

Abstract: A method for treating a primary central nervous system lymphoma in an individual relates to administering intrathecally or intralesionally a therapeutically effective amount of a Fascross-linking composition

thereby inducing the lymphoma cells to undergo Fas-mediated cytotoxicity. The Fas-cross-linking composition may be an agonist anti-human Fas monoclonal antibody or fragments thereof, soluble Fas-ligand (Fas-L), and a combination thereof. In another embodiment, the lymphoma is pretreated with a composition that enhances Fas-mediated cytotoxicity induced by a Fas-cross-linking composition, followed by treatment with the Fas-cross-linking composition.

METHOD FOR INDUCING APOPTOSIS **OF PRIMARY CENTRAL NERVOUS SYSTEM B CELL LYMPHOMAS...**
Publication (No,Kind,Date), Applic (No,Date):
... **20000328**
Non-exemplary Claims: ...Fas-mediated cytotoxicity is at least one chemotherapeutic agent selected from the group consisting of **adriamycin**, cisplatin, cyclophosphamide, doxorubicin, and dexamethasone...

4/3,K,AB/5
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3175859 IFI Acc No: 9923253
IFI Publication Control No: 9923253
Document Type: C
METHOD FOR INDUCING APOPTOSIS **OF CANCER CELL; ADMINISTERING 2-NITROIMIDAZOLE DERIVATIVES AS ANTICARCINOGENIC AGENT; USE IN COMBINATION WITH OTHER ANTINEOPLASTICS**
Inventors: Furusawa Yoshiya (JP); Kamohara Atsuko (JP); Ohyama Harumi (JP); Saito Mizuho (JP); Yamada Takeshi (JP)
Assignee: Pola Chemical Industries Inc JP
Assignee Code: 05476
Publication (No,Kind,Date), Applic (No,Date):
US 5929104 A **19990727** US 97829879 19970402
Calculated Expiration: 20170402
Document Type: CERTIFICATE OF CORRECTION
Certificate of Correction Date: 20020827
Priority Applic(No,Date): US 97829879 19970402

Abstract: Disclosed herein are a method for inducing **apoptosis** of cancer cells, which comprises administering an effective amount of a 2nitroimidazole derivative represented by the general formula (1):

FIG-01

wherein R represents an alkyl, alkenyl or alkynyl group substituted by 1 to 3 hydroxyl groups, and a method for treating a cancer, which comprises using the method for inducing **apoptosis** in combination with another means for killing cancer cells.

METHOD FOR INDUCING APOPTOSIS **OF CANCER CELL...**
Publication (No,Kind,Date), Applic (No,Date):
... **19990727**

Abstract: Disclosed herein are a method for inducing **apoptosis** of cancer cells, which comprises administering an effective amount of a 2nitroimidazole derivative represented by...

...groups, and a method for treating a cancer, which comprises using the

method for inducing **apoptosis** in combination with another means for killing cancer cells.

Exemplary Claim: D R A W I N G

1. A method for inducing **apoptosis** of cancer cells which are treatable by hyperthermia or chemotherapy in a patient in need...

Non-exemplary Claims: ...chemotherapeutic agent is selected from the group consisting of cisplatin, 5-fluorouracil, futraful, mitomycin and **adriamycin** , and said cancer is limited to cancers which respond to treatment with said chemotherapeutic agent.

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